REMARKS

I. Introduction

In response to the Office Action dated February 4, 2008, claims 16, 17, 18, 20, 21, 22, 23 and 24 have been cancelled and claim 14 been amended. Claims 14, 15, 19, 25 and 26 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Claim Amendments

In order to further the prosecution of the instant application, Applicants' attorney has cancelled claims 16, 17, 18, 20, 21, 22, 23 and 24. These claims are cancelled with traverse and without acquiescence to any rejection made by the Patent Office. Applicants reserve the right to pursue the subject matter of these cancelled claims in a continuation application. Applicant has also amended claim 14 as indicated above. This amendment to claim 14 is fully supported by the specification as filed and introduces no new matter. In particular, the amendment to independent claim 14 simply introduces the elements previously recited in dependent claim 24 (now cancelled). The amendment to claim 14 is made with traverse and without acquiescence to any rejection made by the Patent Office. Applicants reserve the right to pursue the subject matter of original claim 14 in a continuation application.

III. Non-Art Rejections

A. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

On page (2) of the Office Action, claims 14-26 were rejected under 35 U.S.C. §112, first paragraph. In this rejection, the Patent Office asserts that the specification, while enabling topiramate, does not provide sufficient information so that all compounds encompassed by the generic compound of formula I of claim 14 are capable of treating dyskinesia.

Applicants respectfully traverse this rejection in view of the specification's description of the well known characteristics of formula I compounds (see, e.g. paragraph [0016]) and the associated animal model used to evaluate compounds within this formula in paragraphs [0070]-[0094]), a disclosure which allows one of skill in the art to evaluate any compound in Formula I with minimal experimentation. In this context, as noted for example In re Wands, courts recognize that the

routine experimentation undertaken to ascertain various unpredictable factors (e.g. the activity of a specific formula I species) is not fatal to a finding of enablement. Specifically, court decisions confirm that the Section 112 enablement requirement implicitly tolerates a disclosure requiring "experimentation" to make or use the claimed invention so long as the experimentation is not "undue" or "unreasonable." In an enablement rejection based on undue experimentation, the focus is not on the need for experimentation per se, but rather undue experimentation. In this context, all that is required is a disclosure which allows one to make and use the invention as broadly as it is claimed. The following analysis of Applicants' disclosure in view of the factors articulated in *In re Wands* reveals that given the specification disclosure, it does not require undue experimentation to make and use compounds encompassed by the generic compound of formula I, as claimed.

In considering the quantity of experimentation necessary to practice the claimed invention, Applicants note that experiments in this art merely involve the examination of a candidate compound encompassed by the generic compound of formula I. Applicants respectfully point out that, given the positive controls and in vivo assays described in the specification, this will require limited experimentation. Therefore, the quantity of experimentation necessary to characterize a formula I compound as claimed is by no means undue. In assessing the amount of direction or guidance presented, Applicants note that the methods disclosed in the specification can be used to assess any formula I compound. Consequently, Applicants' disclosure provides ample guidance for practicing the invention as claimed. In considering the number of working examples provided in the instant disclosure, Applicants note that the specification identifies a number of exemplified compounds, each of which represents a working example thereby providing support for the enablement of the claimed embodiments. In considering the nature of the claimed invention, Applicants note that the assays disclosed in the specification are routine in this art. Moreover, the relative skill of those in this art is quite high. Practitioners of this art customarily have advanced degrees and years of laboratory experience. In addition, numerous treatises on the methods of this art have been published and are widely disseminated. Consequently, both the nature of the invention as discussed above as well as the state of the art in this field support the enablement of Applicants' claims. In considering the breadth of the claims, Applicants' claims are directed to formula I compounds as identified in the specification. The scope of the claims is thereby commensurate with the teachings of the specification. A final factor articulated in *In re Wands* is the predictability or unpredictability of the

art. Because the specification teaches assays that allow artisans how to readily identify compounds within the scope of claim 14, any issue regarding predictability is obviated. Consequently, Applicants' disclosure allows one to make and use the invention as broadly as it is claimed

For the reasons noted above, Applicants respectfully request a withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

B. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

On page (6) of the Office Action, claim 23 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants cancellation of claim 23, with traverse, and without acquiescence to this rejection, renders this rejection moot.

IV. Prior Art Rejections

A. On page (7) of the Office Action, claims 14-18 and 23 were rejected under 35 U.S.C. §102(b) as being anticipated by Shank et al., WO 00/61138 (Shank).

Independent claim 14 has been amended hereinabove to introduce the elements previously recited in dependent claim 24. The subject matter of claim 14 is therefore now focused on dyskinesias that arise as a side effect of a therapeutic agent and does not encompass the clinical management of movement disorders *per se* as contemplated in Shank *et al.* Acknowledging this, claim 24 was not rejected under 35 U.S.C. §102(b) by the Patent Office as being anticipated by Shank. Consequently, Applicants amendment to claim 14, with traverse, and without acquiescence to this rejection, renders this rejection moot.

B. On page (8) of the Office Action, claims 14, 21, 22, and 24 were rejected under 35 U.S.C. §102(b) as being anticipated by Dursun et al., Canadian Journal of Psychiatry, 2000 (Dursun).

Applicants respectfully traverse these rejections because for example, one of skill in the art would not agree with the Patent Office's belief that myoclonic jerks (as disclosed in Dursun) and dyskinesias (as recited in independent claim 14) are identical clinical conditions. Instead, a skilled artisan (i.e. a clinician who treats movement disorders such as Parkinson's disease) would clearly understand that dyskinesias and myoclonic jerks are distinct clinical phenomena. In particular, as shown by the definition of dyskinesia provided in Attachment A from the Parkinson's disease website (www.parkinson.org, an authoritative source of definitions in the movement disorder field), dyskinesias are clinically defined as: "abnormal, involuntary body movements that can appear as jerking, fidgeting, twisting, and turning movements". In contrast myoclonic jerks are a separate clinical phenomena, one characterized by sudden contractions of the big body muscles. Myoclonic jerks typically occur when a subject is falling asleep and cause a feeling of stumbling, falling or similar that subsequently cause a subject to wake up again. While almost everyone has experienced a myoclonic jerk while falling asleep, this experience does not result in a diagnosis of dyskinesia. In view of such differences between these two phenomena, one of skill in the art would not agree with the Patent Office's belief that myoclonic jerks and dyskinesias are identical clinical conditions (as required for a finding of anticipation under 35 U.S.C. §102(b)).

In summary, Dursun teaches a method for the reduction of myoclonic jerks following treatment with clozapine. Dursun *et al.* do not teach or suggest a method for the reduction of dyskinesias, much less a treatment regimen for dyskinesias that arise as a side-effect of a therapeutic agent. For this reason, the Dursun disclosure cannot anticipate the claimed invention. Specifically, anticipation under 35 U.S.C. § 102 has strict requirements that all elements of the claim must be found in a single reference in order to support an anticipation rejection (see e.g. M.P.E.P. 2131). In this context, because Dursun *et al.* fails to teach or suggest the invention recited in claim 14 as amended hereinabove (i.e. a treatment regimen for dyskinesia that arises as a side-effect of a therapeutic agent), Applicants respectfully request a withdrawal of the rejection under 35 U.S.C. §102(b).

C. On page (9) of the Office Action, claims 19, 20, 25, and 26 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dursun as applied to claims 14, 21, 22, and 24 in view of Wolters et al., CMAJ, 1989 (Wolters).

Applicants respectfully traverse these rejections because for example, one of skill in the art would not agree with the Patent Offices assertion that clinicians are motivated to mix and match: (1) the pathologies and therapeutic agents that Dursun teaches are associated with schizophrenia; with (2) the pathologies and therapeutic agents that Wolters teaches are associated with Parkinson's disease in order to generate the invention recited in claim 14 as amended hereinabove.

As noted above, those of skill in this art understand that myoclonic jerks are a different clinical phenomena from dyskinesia as recited in claim 14. One of skill in the art further understands that schizophrenia (as disclosed in Dursun) and Parkinson's disease (as disclosed in Wolters) are very different pathological conditions that result from different underlying physiological mechanisms in the brain. For example as noted in the Wolters disclosure, Parkinson's disease is a pathological condition characterized by decreased dopaminergic activity in the brain (see, e.g. Wolters et al., the paragraph bridging pages 507-508). In contrast, those of skill in the art understand that schizophrenia is a pathological condition characterized by increased dopaminergic activity in the brain (see, e.g. the abstract of Rao et al., Eur Arch Psychiatry Neurol Sci. 1984; 234(1): 8-12, a copy of which is provided as Attachment B). For this reason, the artisan concurrently understands that the clinical regime for the treatment of dyskinesias which arise as a side-effect of a therapeutic agent, requires a distinct clinical regime from the clinical regime required for the treatment of schizophrenics exhibiting myoclonic jerks caused by clozapine (as disclosed in Dursun).

Because of, for example, the very different dopaminergic activity profiles that are observed to occur in the brain in individuals suffering from Parkinson's disease as compared to those suffering from schizophrenia, one of skill in the art would not agree with the Patent Office's belief that artisans are motivated to mix and match therapeutic agents in these different pathologies such that "it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the combination therapy taught by Dursun and applied it to treating Parkinson's disease and the dyskinesia-like side effects caused by L-DOPA as taught by Wolters" (Office Action page 10). Instead, in view of the "opposite" dopaminergic brain profiles known to characterize these two pathological conditions, one of skill in the art would more likely believe that an agent observed to be

useful to treat a patient suffering from Schizophrenia (i.e. having an increased dopaminergic activity in the brain) would be unsuitable for a patient with Parkinson's disease (i.e. having an decreased dopaminergic activity in the brain). In fact, because Schizophrenia and Parkinson's disease a exhibit these "opposite" profiles of dopaminergic activities in the brain, the artisan familiar with this difference between these pathological conditions is taught away from combining the Dursun and Wolters disclosures.

A reference's disclosure teaches away if a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference. *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994). As noted in M.P.E.P. 2145(X)(D)(2), references cannot be combined where reference teaches away from their combination. In this context, because skilled artisans are aware that Schizophrenia and Parkinson's disease exhibit "opposite" profiles of dopaminergic activities in the brain, one of skill in the art would be would be discouraged from mixing and matching therapeutic agents used to treat schizophrenia with agents used to treat Parkinson's disease. For this additional reason, one of skill in the art would not combine the disclosure in Dursun with the disclosure in Wolters to arrive at the invention recited in claim 14. For these reasons, Applicants respectfully request a withdrawal of the rejection under 35 U.S.C. §103(a).

In addition, the various elements of Applicants' claimed invention together provide operational advantages over Dursun and Wolters. In addition, Applicants' invention solves problems not recognized by Dursun and Wolters. Thus, Applicants submit that independent claim 14 is allowable over Dursun and Wolters. Further, the dependent claims are submitted to be allowable over Dursun and Wolters in the same manner, because they are dependent on the independent claims, and thus contain all the limitations of the independent claims. In addition, the dependent claims recite additional novel elements not shown by Dursun and Wolters.

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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WJW/bjs

G&C 184.5-US-WO

ATTACHMENT A

About Parkinson Disease
A Primer on Parkinson Disease
Treatment Options
Living with Parkinson Disease
Maintaining Optimum Wellness
Glossary of Terms
UPDRS

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Glossary of Terms

Acetylcholine (noun): a chemical messenger (transmitter) released by cholin *striatum* area of the brain. It is involved in many brain functions, such as memc motor activity. There appears to be an interplay between the actions of acetylcl dopamine.

Action tremor (noun): a tremor that occurs or increases when the hand is mc

Adjunctive (adjective): supplemental or secondary (but not essential) to the Sometimes used to describe medications used to enhance levodopa therapy

Agonist (noun): a chemical or drug that enhances the activity of a neurotrans dopamine

Akinesia (noun): delay in initiating movement; inability to move; "freezing"

Ancillary (adjective): auxiliary; serving as an aid

Antioxidant (noun): an agent that prevents the loss of oxygen in chemical re.

Anxiolytic (noun): an agent or a class of medications that reduce anxiety

Apoptosis (noun): a form of cell death in which cells shrink and disappear. Sc to as "cell suicide". In Parkinson disease, some scientists believe that the nerve *substantia nigra* portion of the brain die by apoptosis.

Ataxia (noun): loss of balance

Athetosis (noun): slow, involuntary movements of the hands and feet

Autonomic nervous system (noun): the system that controls involuntary bo

Blepharospasm (noun): involuntary clinching of the eyelid

Blood-brain barrier (noun): the protective membrane that separates the blo brain tissue

Bradykinesia (noun): slowness of movement

Bradyphrenia (noun): slowness in thought processing

Chorea (noun): excessive involuntary movements, ranging from twisting or w movements of the extremities

Cogwheeling (noun): a ratchet-like movement in the joints, characteristic of

Delusion (noun): false, fixed, idiosyncratic belief, not substantiated by sensor evidence

Dementia (noun): a broad complex of symptoms such as disorientation, confu loss, impaired judgment, and alterations in mood and personality -- which symp from a variety of causes

DNA (deoxyribonucleic acid) **(noun):** the basic chemical substance that makes

Dysarthria (noun): low voice volume or muffled speech

Dyskinesia (noun): abnormal, involuntary body movements that can appear a fidgeting, twisting, and turning movements; frequently induced by medications Parkinson patients. Dystonia, athetosis, and chorea are forms of dyskinesias

Dysphagia (noun): difficulty in swallowing

Dystonia (noun): involuntary spasms of muscle contraction which cause abno and postures

Endogenous (adjective): originating internally; developing from within, rathe external factors; the opposite of exogenous

Essential tremor (ET) (noun): a condition more common than Parkinson dise includes shaking of the hands or head, and an unsteady quality of the voice

Etiology (noun): the causes or origins of a disease. The etiology of Parkinson known.

Exogenous (adjective): originating externally; arising from external rather th factors; the opposite of endogenous

Festination (noun): short, shuffling steps

ATTACHMENT B

1: Eur Arch Psychiatry Neurol Sci. 1984;234(1):8-12.

Links

Altered interrelationship of dopamine, prolactin, thyrotropin and thyroid hormone in schizophrenic patients.

Rao ML, Gross G, Huber G.

Increased dopaminergic activity has been postulated to be one of the main causes of schizophrenia. To evaluate this hypothesis further, the interrelation between dopamine, prolactin, thyrotropin (TSH) and L-thyroxine was studied by determining their concentrations in the serum of ten acutely ill schizophrenic patients exhibiting distinct stages of process activity and ten healthy subjects. The level of dopamine was elevated in the sera of schizophrenic patients, whereas the levels of prolactin, TSH and L-thyroxine were decreased. On the basis of these results we hypothesize that 1. increased dopaminergic activity affects pituitary secretory function, and 2. decreased beta-adrenergic activity may be a consequence of decreased thyroid hormone concentration in plasma.

PMID: 6489401 [PubMed - indexed for MEDLINE]